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09/889,491	02/05/2002	Philip Kusk	8969-029	4096

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,491	KUSK, PHILIP	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004 and 03 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-30* is/are pending in the application.

4a) Of the above claim(s) *26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is written in response to applicant's submissions filed 7/1/04 and 8/3/04. All previously pending claims have been cancelled and claims 25-30 have been added. New rejections are set forth to address the newly added claims. Applicant's arguments are addressed after all of the rejections are set forth. **This action is FINAL.**

Election/Restrictions

2. The restriction requirement in this application required applicant to select a SINGLE COMBINATION of polymorphisms for search and examination in this application (see p. 2 of the restriction requirement mailed 5/20/03). Applicant elected group I and further elected a polymorphism within BSP. The examiner rejoined an additional polymorphism within BSP in the first office action. Therefore, instantly pending claims 26, 27, and 28 which introduce further combinations of polymorphisms for consideration are non-elected inventions and are withdrawn from prosecution. Claims 25, 29, and 30 are examined herein. Following the guidance set forth in MPEP 803.04, section (C), if a claim reciting the elected combination is found to be allowable, rejoinder of claims which encompass the elected combination (in this case claims 26, 27, and 28) will be appropriate.

Sequence Rules

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s):

Newly added claim 25 recites SEQ ID NO: 18 and SEQ ID NO: 19. These sequences are not represented in the sequence listing. The paper copy of the sequence listing and the CRF filed 2/25/02 have only seventeen total sequences.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit a new CRF and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112-New Matter

4. Claims 25, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "BSP II" in claim 25 appears to represent new matter. The response filed 7/1/04 states that basis for this amendment is found at page 6 lines 15-25 of the specification. However, these lines of the specification do not recite the identifier "BSP II," and a review of the specification did not result in the identification of any other portion of the specification that provides basis for this identifier. Since no basis has been

identified, the claims are rejected as incorporating new matter. Claims 29 and 30 depend from claim 25 and are rejected for having this same subject matter by virtue of their dependency.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 25, 29, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is indefinite because the preamble of the claim recites a much broader scope that the final process step of the claim, and it is not clear how the two are related. The preamble of the claim recites assessing an individual's predisposition to "a selected calcification status" yet the claim recites associating the presence of particular alleles with "a predisposition to a lower peak bone mass." It is not clear if applicant's intention is for the claim to be limited to assessing a predisposition to lower peak bone mass (i.e. that lower peak bone mass is the "selected calcification status") or if the claim is intended to encompass assessing to a predisposition to any calcification status. There is not a nexus between the preamble and the process steps, and this makes the claim confusing. The remaining rejected claims depend from claim 25 and are indefinite over this same recitation.

Claim 25 is indefinite over the recitations of "lower peak bone mass" because "lower" is a relative term and there is no standard as to what the peak bone mass is "lower" than. For example, is the particular allele associated with a predisposition to "lower" peak bone mass relative to a known standard, relative to that of individuals with a different genotype, etc. Claims 28 and 29 are also indefinite over this recitation.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 25, 29, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

MPEP 608.01 (p)[R-2] teaches that "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention."

The newly filed claims recite "the sequence of said gene having GenBank accession number L24756." These claims differ from the previously examined claims in many respects, but for this rejection, the significant difference is the inclusion of a specific reference to a GenBank accession number in the claim. This recitation constitutes an attempt to incorporate by reference to the accession number the subject matter which is contained within the recited GenBank record. This recitation constitutes an improper incorporation by reference of essential material since it is material that is necessary to describe the claimed invention. Essential material may not be incorporated by reference to non-patent publications (MPEP 608.01)(p).

Therefore, the claims are rejected for failure to comply with the enablement requirement because the specification fails to provide essential subject matter for the practice of the claimed invention.

This rejection can be overcome by deleting the specific reference to the GenBank record from the claim. If applicant desires to refer to the full length sequence contained in the GenBank records within the body of the claim, it is recommended that applicant enter this sequence into the sequence listing and refer to the sequence using a proper sequence identifier. It is noted that a declaration has been filed which established the sequence in the GenBank record at the time of filing (see Declaration filed 8/3/04).

9. Claims 25, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method which determines that an individual having a "G" at the BSP-A1496G polymorphism and/or an "A" the BSP-G1869A polymorphism is more likely to have increased bone mass compared to individuals who have an "A" at the BSP-A1496G polymorphism or a "G" at the BSP-G1869A polymorphism of the bone sialoprotein gene, does not reasonably provide enablement for methods which assess an individual's predisposition to the broadly recited "calcification condition status." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is applied to the newly filed claims insofar as they remain indefinite as to the scope of the encompassed "selected calcification condition status."

Nature of the Invention

The invention is concerned with providing a method for assessing an individual's predisposition to a calcification condition status via the genotyping of the promoter of the bone sialoprotein gene. Thus, the practice of the method relies on the showing of an association between a particular genotype and a particular calcification condition status.

The rejected claims are drawn to methods for assessing an individual's predisposition to a selected calcification condition status, which method comprises determining the genotype of the promoter of the bone sialoprotein gene. The preamble of the claims broadly recites assessing an individual's predisposition to "a selected calcification condition status."

Breadth of the claims

Thus, the rejected claims encompass determining a predisposition to any "calcification condition status" which could include a wide variety of diseases, disorders, and phenotypes including, for example, osteoporosis, atherosclerosis, bone mineral density, rate of bone loss, placenta calcification, renal calcification, calcification of tendons or cartilage, etc. The final process step of the claims recites associating an allele with a predisposition to "lower peak bone mass" but it is not clear from the language of the claims that this is the "selected calcification condition status" recited in claim 1, or if the claim encompasses drawing conclusions about any calcification condition status based on the methods of the claims.

Teachings in the Specification and Working Examples

The specification provides two novel polymorphisms within the 5' untranslated region of a gene taught by Kim *et al.* and referred to as the human bone sialoprotein promoter sequence, see GenBank L24756. Within this sequence, applicant identified polymorphisms at positions

1496 (A→G) and 1869 (G→A) wherein the first version is the version present in the published sequence and the second allele is the alternate allele identified by applicant (p. 7, lines 21-30). The specification refers to these variations as BSP-A1496G and BSP-G1869A, respectively.

In example 1 of the specification (beginning on page 22), applicant teaches the screening of the DNA from 133 women for the polymorphisms, via amplification of fragments of DNA and restriction digestion. For the BSP-A1496G polymorphism, SEQ ID NO: 1 and SEQ ID NO: 2 were used as amplification primers, and for the BSP-G1869A polymorphism, SEQ ID NO: 3 and SEQ ID NO: 4 were used as amplification primers (p. 23-24). The specification teaches that for the BSP-A1496G polymorphism, the "A" allele was most abundant, and for the BSP-G1869A, the "A" allele was also more abundant (p. 29). Further, the example demonstrates that there is a significant association between these polymorphisms and bone mass as represented by bone mineral content and bone mineral density measurements (p. 31). Specifically, patients with the "A" allele at 1469 and/or the "G" allele at 1869 are more likely to have higher bone mass than patients with the opposite alleles (p. 31-32). Further the specification specifically states that the polymorphisms did not appear to have a statistically significant impact on the change in bone mass over time (see p. 32), and that the observations presented strongly indicate that the BSP polymorphisms influence peak bone mass rather than the rate of bone loss (p. 32, lines 18-20).

The specification does not provide any evidence or disclosure that these polymorphisms are associated with any additional phenotypes related to calcification status, or any showing that these two disclosed polymorphisms are related to all indicators of calcification status or all disease which are related to calcification status. While low bone mass is an indicator of osteoporosis accepted in the prior art, the specification does not provide any guidance as to

whether any of the bone masses observed in the instant study were sufficiently low so as to be indicators of such a disease or a predisposition to such a disease as no data is given as to the bone mass of the patients at particular ages or compared to other patients.

State of the prior art and Level of unpredictability

The prior art is silent as to polymorphisms within any bone sialoprotein gene promoter.

However, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms (such as the two recited in the instant claims) would be associated with any phenotypic trait, such as a disease state or a physiological state. The instant specification demonstrates this unpredictability by demonstrating that the BSP polymorphisms are associated with peak bone mass but not with rate of bone loss. The prior art further exemplifies such unpredictability. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated

and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed that the two polymorphisms in the promoter of a human bone sialoprotein gene are associated with peak bone mass, it remains highly as to which additional phenotypes the disclosed polymorphisms may be associated with. Thus, the claimed method directed towards the assessment of a predisposition to a selected calcification condition status requires the knowledge of unpredictable and potentially non-existent associations between the instantly disclosed polymorphisms and additional calcification condition statuses.

Quantity of Experimentation

The practice of the claimed invention commensurate in scope with the instant claims would require a high degree of experimentation to associate the disclosed polymorphisms with any or all calcification condition statuses. With respect to the disclosed polymorphisms within the bone sialoprotein gene, the practice of the claimed invention would require extensive further work to determine which calcification conditions can be predicted using even these polymorphisms. That this work would be unpredictable is exemplified in the specification which

demonstrates that while the two disclosed polymorphisms may be predictors of bone mass within the tested population, they are not predictors of the rate of bone loss.

Conclusion

Thus, having considered each of these factors, namely the breadth of the claims, the high level of unpredictability in the related art, the lack of guidance in the specification and the prior art, and the high quantity of experimentation, it is concluded that it would require undue experimentation to practice the claimed invention commensurate in scope with the instant claims.

Response to Remarks

112, 2nd paragraph rejections

The cancellation of the previously pending claims and presentation of new claims renders the previous rejections moot. However, some of the issues raised in the newly set forth rejections are similar to the previous rejections, and for these, applicant's remarks are addressed.

Applicant states that "new claim 25 features specific determination and association steps that point out the intended method with ample precision (p. 6, second full ¶)." However, this is not persuasive, for the reasons stated in the rejection set forth herein. Namely, the claims remain confusing because the preamble is of much broader scope that the process steps set forth in the claim, and it is not clear which scope applicant is trying to capture.

The rejections in view of the recitation of "the bone sialoprotein gene" are overcome in the new claim. The rejection is overcome by the recitation of particular portions of the gene in question (the specific sequences in SEQ ID NO: 13, 14, 18, and 19) which in concert with the recitation "the bone sialoprotein gene" would make clear to one practicing the invention which

nucleic acid is intended. The deletion of the recitation "BSP II" from this claim would overcome the issue of new matter raised in this office action and would still result in the meaning of "the bone sialoprotein gene" remaining definite.

Applicant's position regarding the potential 112 2nd in view of the recitation of the GenBank Accession number L24756 in the claim has been considered. No 112 2nd ¶ rejection is set forth in view of applicant's arguments on page 7 of the response, in view of the fact that prior to filing of this application a single sequence was disclosed in any version of the GenBank record, and in view of the recitation of specific sequences within the claim which give context to the location of the polymorphism within the bone sialoprotein gene.

In the first full paragraph on page 9 of the response filed 7/1/04, applicant states that new claim 25 addresses the issue of "lower peak bone mass" being indefinite, but does not explain how this issue is addressed. The rejection is applied to the newly filed claims in view of the identical language appearing in the newly added claims.

112, 1st paragraph rejections

The written description rejection is withdrawn because the newly filed claims are limited to the determination of the genotype of very specific polymorphisms within the bone sialoprotein gene promoter which are identified within a very particular sequence context.

With regard to the enablement rejection, applicant states that "the Office position regarding the "breadth of the claims" on p. 11 is moot in view of this submission (p. 9 of response, 5th full ¶)." However, the examiner does not agree since the claims are unclear as to whether they are meant to encompass assessing a predisposition to any selected calcification

condition status or to only a predisposition to a "lower" peak bone mass. Therefore, the rejection is applied to the newly added claims.

Rejection under 102(b)

The rejection is overcome by the additional steps which were added to newly filed independent claim 25.

Note

It is noted that there is no literal antecedent basis for the phrase "said amplified portion" in claim 30. No rejection under 112 2nd paragraph has been set forth because it is clear from the language of the claim that applicant is referring to the "relevant portion" of the DNA of the gene promoter that was amplified in claim 29. However, it would be even more clear if claim 29 were amended to recite "thereby producing an amplified portion" at the end of the claim.

Conclusion

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Juliet C. Switzer
Examiner
Art Unit 1634

October 11, 2004